Warner-Lambert Company
170 Tabor Road
Morris Plains, NJ 07950

Phone: 973-540-2000
Fax: 973-540-3761
Internet: http://www.warner-lambert.com

WARNER LAMBERT

November 17, 1999

Charles Ganley, M.D.
Director
Division of Over-the-Counter Drug Products (HFD-560)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, Building Two
Rockville, MD 20850

Attention: Dockets Management Branch
Food and Drug Administration
Room I-23
12420 Parklawn Drive
Rockville, MD 20857

Subject: **Pre-meeting Materials for December 3, 1999 Feedback Meeting.**

Docket No. 80N-0042.
"Anticaries Drug Products for Over-the-Counter Human Use; Final Monograph," 60(194) *Federal Register 52474-52510,* October 6, 1995.

Docket No. 81 N-0033.
"Over-the-Counter Dental and Oral Health Care Drug Products for Antiplaque Use; Safety and Efficacy Review," 55(182) *Federal Register* 38560-38562, September 19, 1990.

Dear Dr. Ganley:

Thank you for the upcoming feedback meeting on Friday, December 3, 1999. We also thank you for the previous feedback meeting on October 8, 1999.

This submission is the pre-meeting package for the December 3 meeting.

As submitted in our previous, September 14 pre-meeting package and discussed at the October 8 meeting, we seek to amend the final rule for anticaries drug

80N-0042

RPT8

products.' It is our intention to submit a Citizen Petition' to provide for an alternate dose and pH for an acidulated phosphate fluoride treatment rinse containing 0.01% fluoride ion.[3] The directions for use in the current final rule direct consumers to rinse with ten milliliters of the treatment rinse for sixty seconds,[4] and the product is formulated to pH 3.5. We will petition to amend the rule to provide for an alternate dose of twenty milliliters for thirty seconds, and the product will be formulated at pH 4.2.

The specific outcomes we desire from the December 3 meeting follow.

First, it is our intention to conduct a human study demonstrating that the proposed alternate dose is effective. Efficacy[5] will be demonstrated by showing that salivary fluoride levels obtained from rinsing with ten milliliters of pH 3.5 treatment rinse for sixty seconds are comparable to the salivary fluoride levels obtained from rinsing with twenty milliliters of pH 4.2 treatment rinse for thirty seconds. These study results will be the basis for the Citizen Petition to amend the monograph.

We seek Agency review and comment on the study protocol following this letter, such that we may have the reasonable belief that successful completion of the planned study will provide the basis for favorable Agency action on the planned Citizen Petition.

Second, as we are requesting only a minor dosing and pH change to the final rule, we seek Agency agreement that no additional safety studies are required. We seek Agency agreement that the requirement to demonstrate that the alternate dose is safe[6] will be addressed by (1) a comprehensive safety summary, and (2) successful completion of the planned human study showing that the retained salivary fluoride levels are the comparable between the two dosing regimens.

These two items are discussed individually below.

---

1 "Anticaries Drug Products for Over-the-Counter Human Use," 21 CFR § 355.
For convenience, the rule is presented as Attachment 1.
"Anticaries Drug Products for Over-the-Counter Human Use; Final Monograph," 60(194) Federal Register 5247452510, October 6, 1995.

2 21 CFR § 330.10(a)(12)(i) and § 10.30.

3 21 CFR § 355.1 0(a)(3)(ii).

4 21 CFR § 355.50(d)(2)(ii).

5 21 CFR § 330.10(a)(4)(ii).

6 21 CFR § 330.1 O(a)(4)(i).

Efficacy of the Acidulated Phosphate Fluoride Treatment Rinse

As stated above, it is our intention to conduct a study to evaluate the human salivary fluoride levels between two doses for an acidulated phosphate fluoride anticaries treatment rinse. The protocol for the planned study is submitted as Appendix 1, and we request Agency review the appended protocol.

We have conducted additional studies to show that the test product is an effective anticaries treatment rinse. A summary of the completed studies and the rationale for the human salivary fluoride level study is stated in a Technical Summary presented as Appendix 2.

The Technical Summary describes the studies which both (1) demonstrate that the test anticaries treatment rinse is effective, and (2) support the selection of the salivary fluoride level study as appropriate for the petition to amend the monograph.

The studies that conclusively demonstrate that the fluoride in the test product is available for anticaries benefit are a rat caries study, an enamel solubility reduction study, and an enamel fluoride uptake study. Final reports for these studies are submitted for Agency review as Appendices 3, 4, and 5, respectively.

Having demonstrated that the fluoride is available, we then conducted an exploratory salivary fluoride level study, as also described in the Technical Summary. The very favorable results are presented in the report of the pilot study, which is submitted as Appendix 6. This pilot study is the basis for the planned, larger salivary fluoride level comparability study submitted in Appendix 1.

Safety of the Acidulated Phosphate Fluoride Treatment Rinse

We are requesting a minor change to the anticaries final rule. As such, no additional safety studies are planned. The planned human salivary fluoride level study will also demonstrate the safety of the alternate dose. If the salivary fluoride levels are comparable, no additional safety questions are raised by the alternate dose.

Meeting Participants

Participants representing Warner-Lambert Consumer Healthcare at the December 3 meeting will include:

Michael Barnett, D.D.S., Senior Director, Dental Affairs;
Janet Firriolo, Ph.D., Senior Manager, Toxicology;

Scott Harper, Ph.D., Director, Dental Affairs;
Lori Kumar, Ph.D., Director, Oral Care Research and Development;
J. Tony McGuire, Ph.D., Senior Manager, Statistics and Data Management; and
Paul Okarma, Ph.D., Director, Regulatory Affairs.

Dr. Dominick Zero, Director, Oral Health Research Institute, Indiana University School of Dentistry will also attend the meeting at our invitation. He is the Principal Investigator for the planned human salivary fluoride level study.

If you have any questions or would like any additional information in advance of the feedback meeting, please contact Paul Okarma, Ph.D., Director, Regulatory Affairs, directly. His direct-dial telephone number is (973) 385-5031.

We look forward to a very productive meeting.

Respectfully,

Judith M. Sills, Pharm.D.
Senior Director
U.S. Regulatory Affairs
and Global Product Safety

JMS:pjo

Attachments

Desk copies (12) to
Mr. Kerry Rothschild, HFD-560

Appendices

Appendix 1 Clinical Protocol 936-9201

"Comparisons of Two Dosing Regimens of a Fluoride Mouthrinse Prototype (W2194-462) Using Salivary Fluoride Clearance," Consumer Healthcare Research and Development, Warner-Lambert Company. November 12, 1999

Appendix 2 Technical Summary

"Fluoride Testing of Experimental Acidulated Phosphate Fluoride Mouthrinses Containing 0.01% Fluoride Ion and Listerine Essential oils."

Appendix 3 Research Report 936-0115

"Anticaries Efficacy in Rats of Experimental Fluoride Mouthrinse Formulations W2194-462 and W2194-461 and Controls (Study 936-9170)," Consumer Healthcare Research and Development, Warner-Lambert Company, November 10, 1999.

Appendix 4 Research Report 936-9109

"Dental Enamel Solubility Reduction by Experimental Fluoride Mouthrinse Formulations W2194-462 and W2194-461 (Study 936-9176)," Consumer Healthcare Research and Development, Warner-Lambert Company, November 11, 1999.

Appendix 5 Research Report 936-0108

"Enamel Fluoride Uptake from Experimental Fluoride Mouthrinse Formulations W2194-462 and W2194-461 (Study 936-9175)," Consumer Healthcare Research and Development, Warner-Lambert Company, November 11, 1999.

Appendix 6 Research Report 936-0114

"Comparison of Two Dosing Regimens of Fluoride Mouthrinse Prototype (W2194-462) Using Salivary Fluoride Clearance: A Pilot Study," Consumer Healthcare Research and Development, Warner-Lambert Company, November 11, 1999.